Genetic Testing for Diagnosis and Management of Mental Health Conditions

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cytochrome p450 Genotyping is addressed separately in medical policy 00169.

Note: Genetic Testing for Tamoxifen Treatment is addressed separately in medical policy 00269.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for diagnosis and management of mental health disorders in all situations, including but not limited to the following to be **investigational:***

- To confirm a diagnosis of a mental health disorder in an individual with symptoms.
- To predict future risk of a mental health disorder in an asymptomatic individual.
- To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications:
    - selective serotonin reuptake inhibitors
    - selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
    - tricyclic antidepressants
    - antipsychotic drugs.

Based on review of available data, the Company considers genetic testing panels for mental health disorders, including but not limited to the Genecept™‡ Assay, STA^{2}R test, the GeneSight®‡ Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel for all indications to be **investigational.***

Background/Overview

MENTAL HEALTH DISORDERS

Mental health disorders cover a wide range of clinical phenotypes and are generally classified by symptomatology in systems such as the classification outlined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*). In addition to counseling and other forms of behavioral treatment, treatment commonly involves one or more psychotropic medications aimed at alleviating symptoms of the disorder. Although there are a wide variety of effective medications, treatment of mental health disorders is characterized by relatively high rates of inadequate response. This

often necessitates numerous trials of individual agents and combinations of medications to achieve optimal response.

Knowledge of the physiologic and genetic underpinnings of mental health disorders is advancing rapidly and may substantially alter the way these disorders are classified and treated. Genetic testing could be used in several ways, including stratifying patients' risks of developing a particular disorder, aiding diagnosis, targeting medication therapy, and optimally dosing medication.

Pharmacogenomic Testing
The efficacy and toxicity of psychopharmacotherapeutic drugs vary substantially across individuals. Due to these variances, choice of drug and dose are challenging, requiring close monitoring and adjustments, which prolong the time to optimal therapy. In some cases, serious adverse events may result.

Treatment decisions are currently based on the assessment of different factors that may influence the variability of drug effects: age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics studies how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, and decrease medical costs.

Genes Relevant to the Diagnosis and Management of Mental Health Disorders
Below is a brief outline of genes that may be relevant to the diagnosis and management of mental health disorders, which are currently available in genetic testing panels.

ABCB1 Gene
Variants in the *ABCB1* gene encode a P-glycoprotein efflux pump that is involved in the transport of various molecules (including antidepressant drugs), across the blood-brain barrier.

Serotonin Transporter
The serotonin transporter gene (*SLC6A4*) is responsible for coding the protein that clears serotonin metabolites (5-hydroxytryptamine) from the synaptic spaces in the central nervous system. This protein is the principal target for many of the selective serotonin reuptake inhibitors. By inhibiting the activity of the SLC6A4 protein, the concentration of 5-hydroxytryptamine in the synaptic spaces is increased. A common variant in this gene consists of insertion or deletion of 44 base pairs in the serotonin-transporter-linked

polymorphic region. These variants have been studied in relation to a variety of psychiatric and nonpsychiatric conditions, including anxiety, obsessive-compulsive disorder, and response to selective serotonin reuptake inhibitors.

Serotonin Receptor
The serotonin receptor gene (*5HT2C*) codes for one of at least 6 subtypes of the serotonin receptor that are involved in the release of dopamine and norepinephrine. These receptors play a role in controlling mood, motor function, appetite, and endocrine secretion. Alterations in functional status have been associated with affective disorders such as anxiety and depression. Certain antidepressants (eg, mirtazapine, nefazodone) are direct antagonists of this receptor. There is also interest in developing agonists of the 5HT2C receptor as a treatment for obesity and schizophrenia, but such medications are not commercially available at present.

The serotonin receptor gene (*5HT2A*) codes for another subtype of the serotonin receptor. Variations in the *5HT2A* gene have been associated with susceptibility to schizophrenia and obsessive-compulsive disorder and response to certain antidepressants.

Sulfotransferase Family 4A, Member 1
The sulfotransferase family 4A, member 1, gene (*SULT4A1*) encodes a protein involved in the metabolism of monoamines, particularly dopamine and norepinephrine.

Dopamine Receptors
The *DRD2* gene codes for the D2 subtype of the dopamine receptor. The activity of this receptor is modulated by G proteins, which inhibit adenyl cyclase. These receptors are involved in various physiologic functions related to motor and endocrine processes. The D2 receptor is the target of certain antipsychotic drugs. Variants in this gene have been associated with schizophrenia and myoclonic dystonia. Variants of the *DRD2* gene have also been associated with addictive behaviors (eg, smoking, alcoholism).

The *DRD1* gene encodes another G protein–coupled receptor that interacts with dopamine to mediate some behavioral responses and to modulate D2 receptor–mediated events. Variants of the *DRD1* gene have been associated with nicotine dependence and schizophrenia.

The *DRD4* gene encodes a dopamine receptor with a similar structure; *DRD4* variants have been associated with risk-taking behavior and attention-deficit/hyperactivity disorder.

Dopamine Transporter
Similar to the *SCL6A4* gene, the dopamine transporter gene (*DAT1* or *SLC6A3*) encodes a transporter that mediates the active reuptake of dopamine from the synaptic spaces in the central nervous system. Variants in this gene are associated with Parkinson disease, Tourette syndrome, and addictive behaviors.

Dopamine β-Hydroxylase
The dopamine β-hydroxylase (*DBG*) gene encodes a protein that catalyzes the hydroxylase of dopamine to norepinephrine. It is primarily located in the adrenal medulla and postganglionic sympathetic neurons. Variation in the *DBH* gene has been investigated as a modulator of psychotic symptoms in psychiatric disorders and tobacco addiction.

Gated Calcium Channel
The gated calcium channel gene (*CACNA1C*) is responsible for coding of a protein that controls activation of voltage-sensitive calcium channels. Receptors for this protein are found widely throughout the body, including skeletal muscle, cardiac muscle, and in neurons in the central nervous system. In the brain, different modes of calcium entry into neurons determine which signaling pathways are activated, thus modulating excitatory cellular mechanisms. Associations of variants of this gene have been most frequently studied in relation to cardiac disorders. Specific variants have been associated with Brugada syndrome and a subtype of long QT syndrome (Timothy syndrome).

Ankyrin 3
Ankyrins are protein components of the cell membrane and interconnect with the spectrin-based cell membrane skeleton. The *ANK3* gene codes for the protein Ankyrin G, which has a role in regulating sodium channels in neurons. Alterations of this gene have been associated with cardiac arrhythmias (eg, Brugada syndrome). Variants of this gene have also been associated with bipolar disorder, cyclothymic depression, and schizophrenia.

Catechol O-Methyltransferase
The catechol *O*-methyltransferase gene (*COMT*) codes for the COMT enzyme, which is responsible for the metabolism of the catecholamine neurotransmitters, dopamine, epinephrine, and norepinephrine. COMT inhibitors (eg, entacapone) are currently used to treat Parkinson disease. A variant of the *COMT* gene, Val158Met, has been associated with alterations in emotional processing and executive function and has also been implicated in increasing susceptibility to schizophrenia.

Methylenetetrahydrofolate Reductase
The methylenetetrahydrofolate reductase gene (*MTHFR*) is a widely studied gene that codes for the protein that converts folic acid to methylfolate. Methylfolate is a precursor for the synthesis of norepinephrine, dopamine, and serotonin. It is a key step in the metabolism of homocysteine to methionine, and deficiency of MTHFR protein can cause hyperhomocysteinemia and homocystinuria. The MTHFR protein also plays a major role in epigenetics, through methylation of somatic genes. A number of variants have been identified that alter the activity of the MTHFR enzyme. These variants have been associated with a wide variety of clinical disorders, including vascular disease, neural tube defects, dementia, colon cancer, and leukemia.

γ-Aminobutyric Acid A Receptor
The γ-aminobutyric acid A (GABA) receptor gene encodes a ligand-gated chloride channel composed of 5 subunits that respond to GABA, a major inhibitory neurotransmitter. Variants in the *GABA* receptor gene have been associated with several epilepsy syndromes.

μ- and κ-Opioid Receptors
OPRM1 encodes the μ-opioid receptor, which is a G protein–coupled receptor that is the primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone. Variants in the *OPRM1* gene have been associated with differences in dose requirements for opioids. *OPRK1* encodes the κ-opioid receptor, which binds the natural ligand dynorphin and a number of synthetic ligands.

Cytochrome P450 Genes
CYP2D6, *CYP2C19*, *CYP3A4*, *CYP1A2*, *CYP2C9*, and *CYP2B6* code for hepatic enzymes that are members of the cytochrome P450 family and are responsible for the metabolism of a wide variety of medications, including many psychotropic agents. For each of these genes, variants exist that affect the rate of enzyme activity, which consequently affect drug metabolization rates. Based on the presence or absence of variants, patients can be classified as rapid metabolizers, intermediate metabolizers, and poor metabolizers. Rapid metabolizers may not benefit from standard therapeutic doses because the drug is metabolized too quickly, resulting in subtherapeutic medication levels. Alternatively, poor metabolizers may require lower doses to avoid adverse events from an excess of medication in their system.

P-Glycoprotein Gene
The *ABCB1* gene, also known as the *MDR1* gene, encodes P-glycoprotein, which is involved in the transport of most antidepressants across the blood-brain barrier. *ABCB1* variants have been associated with differential response to antidepressants that are substrates of P-glycoprotein, but not to antidepressants that are not P-glycoprotein substrates.

UDP-Glucuronosyltransferase Gene
The UDP-glucuronosyltransferase gene (*UGT1A4*) encodes an enzyme of the glucuronidation pathway that transforms small lipophilic molecules into water-soluble molecules. Variants in the *UGT1A4* gene have been associated with variation in drug metabolism, including some drugs used for mental health disorders.

Commercially Available Genetic Tests
Several test labs market panels of tests or individual tests relevant for mental health disorders, which may include a variety of genes relevant to psychopharmacology or risk of mental illness. Some of the panels (eg, the GeneSight panel) provide an overall risk score or summary score.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The tests discussed in this section are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.
Examples of commercially available panels include the following:

- Genecept™‡ Assay (Genomind);
- STA^{2}R test (SureGene Test for Antipsychotic and Antidepressant Response; Clinical Reference Laboratory). Specific variants included in the panel were not easily identified from the manufacturer's website.
- GeneSight®‡ Psychotropic panel (Assurex Health);
- Proove Opioid Risk panel (Proove Biosciences);
- Mental Health DNA Insight™‡ panel (Pathway Genomics);
- IDgenetix-branded tests (AltheaDx).

Also, many labs offer genetic testing for individual genes, including *MTFHR* (GeneSight Rx and other laboratories), *CYP450* variants, and *SULT4A1.*

AltheaDx offers a number of IDgenetix-branded tests, which include several panels focusing on variants that affect medication pharmacokinetics for a variety of disorders, including psychiatric disorders.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

TESTING FOR DIAGNOSIS OR RISK OF MENTAL HEALTH DISORDER

For the first indication, this evidence review will assess whether genetic testing to determine the diagnosis or risk of mental illness is clinically useful. A useful test provides information to make a clinical management

decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Clinical Context and Test Purpose
The purpose of testing for genes associated with increased risk of mental illness in patients who are currently asymptomatic is to identify those for whom an early intervention during a presymptomatic phase of the illness might facilitate improved outcomes.

The question addressed in this evidence review is: Does the use of testing for genes associated with increased risk of mental illness in patients who are currently asymptomatic improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is asymptomatic individuals who would consider an intervention were a genetic variant detected.

Interventions
The intervention of interest is testing for genes associated with increased risk of mental illness, either as a panel or single gene.

Comparators
At present, decisions about management of mental illnesses are made when patients present with symptoms and are typically diagnosed based on clinical evaluation according to standard criteria (ie, *Diagnostic and Statistical Manual of Mental Disorders*).

Outcomes
The primary outcome of interest is change in disease outcomes, which would result directly from changes in management that could be instituted because of earlier disease detection. For many mental illnesses, there are standardized outcome measures (eg, Hamilton Rating Scale for Depression [HAMD]).

Timing
Outcomes occur over the course of years.

Setting
Testing would generally occur in the primary care or mental health practice setting.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Evidence on the clinical validity of genetic testing for mental health disorders consists primarily of genome-wide association studies (GWAS) that correlate specific genetic variants with phenotypes and case-control studies that compared the odds ratio for genetic variants in individuals who had a clinical disorder with individuals who did not. In general, cross-sectional and case-control studies cannot be used to generate diagnostic characteristics such as sensitivity and specificity or clinically relevant risk prediction.

A comprehensive review of the GWAS and case-control studies for all investigated genes and their variants is beyond the scope of this review. In a review of meta-analyses examining the association between specific genes and specific mental health disorders, Gatt et al (2015) reported that 134 genes (206 variants) have been identified as significantly associated risk factors for major depressive disorder, anxiety disorders, attention-deficit/hyperactivity disorder, schizophrenia, or bipolar disorder, with 13 genetic variants shared between 2 or more disorders. Examples of research in this area are summarized in Table1.

Table 1. Evidence for Genes Associated With Mental Health Conditions

Gene	Condition	Evidence	Conclusions
ANK3, *CACNAIC*	Bipolar disorder	• Croarkin (2017), case-control	Initial analysis showed associations with bipolar disorder; associations no longer significant after controlling for multiple comparisons
	Depression	• Kloiber (2012), meta-analysis	Initial analysis showed associations with depression; associations no longer significant after controlling for multiple comparisons
	Schizophrenia	• Jiang (2015), meta-analysis	Variants associated with schizophrenia in both white and Asian populations
COMT	Schizophrenia	• Zammit (2007), case-control	No association detected
DRD1, *DRD2*, *DRD4*, *DAT1* (*SLC6A3*)	Addictive behavior	• Batel (2008), case-control • Du (2011), meta-analysis • Huang (2008), case-control • Stapleton (2007), meta-analysis • Xu (2011), meta-analysis	• *DRD1* variants associated with alcohol dependence • *DRD1* variants associated with tobacco dependence • *DAT1* variant associated with successful smoking cessation

Gene	Condition	Evidence	Conclusions
			• Inconsistent results: some analyses found *DAT1* variants associated with alcohol dependence and some analyses did not
	Bipolar and unipolar disorders	• Lopez Leon (2005), case-control • Zou (2012), meta-analysis	Association with bipolar and unipolar disorders found with 1 of 3 *DRD2* variants tested Initial analysis showed associations with *DRD4* variants; associations no longer significant after controlling for multiple comparisons
	Schizophrenia	• Jonsson (2003), case-control • Liu (2014), meta-analysis • Pan (2014), meta-analysis • Zhu (2011), case-control	• *DRD2* variants associated with schizophrenia in males only • *DRD2* variants associated with schizophrenia in whites, but not in Asians • Some *DRD1* variants associated with increased risk and some *DRD1* variants associated with decreased risk for schizophrenia
MTHFR	Bipolar disorder	• Hu (2015), meta-analysis	Variants marginally associated with bipolar disorder, particularly in Asian and black populations
	Depression	• Bousman (2014), cohort • Lizer (2011), case-control • Wu (2013), meta-analysis	• One variant of several tested may indicate more severe prognosis in patients with depression • Inconsistent results, with some analyses showing variants associated with depression, particularly in Asian populations, and other analyses did not
	Schizophrenia	• Hu (2015), meta-analysis	Variants associated with schizophrenia, particularly in Asian and black populations
	Bipolar disorder, depression, schizophrenia combined	• Peerbooms (2011), meta-analysis	Inconsistent results, with 1 variant associated with the combination of psychiatric conditions, but not with the individual conditions, and other variants not associated with the combination or individual conditions
SLC6A4	Addictive behavior	• Enoch (2011), case-control	Variant associated with alcohol and heroin/cocaine addiction
	Anxiety	• Hariri (2002), case-control • Minelli (2011), meta-analysis • Sen (2004), meta-analysis	Inconsistent results, with variants showing significant associations with some anxiety-related traits (eg, neuroticism, fear), but no association with other traits (eg, harm avoidance)
	Bipolar and unipolar disorders	• Lasky-Su (2005), meta-analysis	Variants associated with bipolar disorder, but not unipolar disorder
	Depression	• Karg (2011), meta-analysis • Kiyohara (2010), meta-analysis • Risch (2009), meta-analysis	Inconsistent results: • When meta-analysis combined significance results, there was an association with the gene, stress, and developing depression; when meta-analysis combined raw data, no association detected • Variant associated with depression in whites, no association in Asians
SULT4A1	Schizophrenia	• Meltzer (2008), case series	All patients in series had schizophrenia; those

Gene	Condition	Evidence	Conclusions
			with variant had worse symptom scores

Subsection Summary: Clinically Valid
The association between mental health disorders and individual gene variants is an area of active investigation. For tests included in currently available genetic testing panels, the largest body of evidence appears to be related to the role of *SLC6A4* and various dopamine receptor gene (*DRD1*, *DRD2*, *DRD4*, *DAT1*) variants and multiple mental health disorders. For these and other gene variants, the association with disease risks appears to be relatively weak and not consistently demonstrated across studies. Studies have not been conducted to determine the diagnostic capability or precise risk prediction, but to determine whether the particular genotype of interest is associated with mental health disorders. Diagnostic characteristics of the genes or validated risk estimates in clinically relevant populations are not available.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Although studies have suggested that there may be a number of genetic variants associated with increased risk of mental health disorders, estimates of the magnitude of the increased risk vary across studies. For the individual tests, results from GWAS and case-control studies are insufficient to determine clinical utility.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

There is no strong chain of indirect evidence supporting the clinical utility of any of the previously mentioned genes associated with disease risk. To determine clinical utility, evidence is needed showing that testing for variants in these genes leads to changes in clinical management that improve outcomes.

Section Summary: Testing for Diagnosis or Risk of Mental Health Disorder
No studies were identified that used genetic tests to diagnose a mental health condition to manage patients. There is no clear clinical strategy for how the associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a specific disorder.

TESTING FOR GENES ASSOCIATED WITH MEDICATION PHARMACOKINETICS AND PHARMACODYNAMICS

For indication 2, this evidence review will assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical uses of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Test Purpose

The purpose of pharmacogenetic testing in patients diagnosed with mental illness is to informmanagement decisions such as starting a particular drug, setting or adjusting a dose, or changing drugs when therapy fails.

The question addressed in this evidence review is: Does psychopharmacologic management aided by genetic testing improve the net health outcome compared with management guided by clinical symptoms alone?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals being managed with psychopharmacologic drugs.

Interventions

Interventions of interest include testing for genes associated with medication pharmacokinetics and/or pharmacodynamics, either singularly or as a panel.

Comparators
Currently, decisions about medication management for mental illnesses are typically made based on clinical response, potentially informed by studies such as the Sequenced Treatment Alternatives to Relieve Depression study, which evaluated specific medication sequences.

Outcomes
The primary outcome of interest is change in disease outcomes resulting from more appropriate selection of specific drugs or doses for the patient's condition. Also, avoidance of adverse events is an important outcome. For many mental illnesses, there are standardized outcome measures (eg, HAMD).

Timing
Outcomes occur over the course of years.

Setting
Testing would generally occur in the primary care or mental health practice setting.

Overview of Pharmacogenetics and Mental Health Disorders
Genetic variants may alter medications' pharmacokinetics (ie, how medications are absorbed, distributed, metabolized, or excreted) or pharmacodynamics (ie, medications' effects on the body); thus, individual genetic differences may lead to variability in the effectiveness of medications used to treat mental health disorders.

A large body of evidence has shown that certain gene variants code for enzymes involved in the metabolism of antipsychotic and antidepressant medications. The evidence consists of systematic reviews, meta-analyses, RCTs, as well as case-control and cohort studies. The largest systematic review, by Altar et al (2013), sponsored by Assurex, the manufacturer of the GeneSight Psychotropic panel, assessed the efficacy and safety of 26 antipsychotic and antidepressant medications associated with variants in 8 genes: *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP1A2*, *CYP3A4*, 2 serotonin receptor genes (*HTR2C*, *HTR2A*), and *SLC6A4*. Reviewers identified 294 studies meeting their inclusion criteria. Table 2 summarizes additional studies investigating the association between genetic variants and medications for mental health conditions.

Table 2. Evidence for Genes Associated With Response to Drug Treatment for Mental Health Conditions

Gene	Condition	Evidence	Conclusions
ABCB1	Depression	• Breitenstein (2015), meta-analysis • Gex-Fabry (2008), cohort	• Meta-analysis showed 2 of 6 variants associated with response to antidepressants • Cohort did not find association between variant and response to SSRI (paroxetine)
DRD1, *DRD2*, *DRD4*, DAiT1 (*SLC6A3*)	Depression	• Yin (2015), RCT	• *DRD4* variants associated with level of response to SSRIs • *DRD2* and *DAT1* variants not associated with response to SSRIs

Gene	Condition	Evidence	Conclusions
	Schizophrenia	• Hwang (2007), case-control • Kaur (2017), case-control • Zhang (2010), meta-analysis	• *DRD1* variants associated with response to antipsychotic drugs among African American samples, but not among whites • *DRD2* variants associated with level of response to antipsychotic drugs
CYP450 (*CYP2D6*, *CYP2C19*, *CYP3A4*)	ADHD	• Fijal (2015), RCT • Ramoz (2009), cohort	• Patients with *CYP2D6* variant metabolizer status of ultrarapid, extensive, and intermediate, have similar safety profiles when treated with SNRI (atomoxetine) • *CYP2D6* variant not associated with response to SNRI (atomoxetine)
	Depression	• Gex-Fabry (2008), cohort • Lloret-Linares (2018), cohort • Lobello (2010), meta-analysis • Serretti (2009), case-control • Taranu (2017), cohort	• Most studies reported variants not associated with response to antidepressants or remission rates • Meta-analysis reported *CYP2D6* variant associated with response to SNRI (venlafaxine)
	Schizophrenia	• Almoguera (2013), case series • Crescenti (2008), case-control • Kaur (2017), case-control • Panagiotidis (2007), case series	• Inconsistent results, with some studies showing *CYP2D6* variants associated with response to antipsychotic (risperidone) and 1 study reporting *CYP2D6* variants associated with serum concentrations of antipsychotic drug (haloperidol), but not with clinical effects as measured by Schizophrenia Syndrome Scale • *CYP2D6* variants associated with antipsychotic-induced extrapyramidal side effects
OPRiM1	Addictive behavior	• Chamorro (2012), meta-analysis	Variant associated with response to opioid antagonist (naltrexone) in patients with alcohol dependence
SLC6A2	ADHD	• Ramoz (2009), cohort	Variant associated with response to SNRI (atomoxetine)
	Depression	• Yin (2015), RCT	Variants not associated with response to SSRIs
SLC6A4	Addictive behavior	• Johnson (2011), RCT	Variant associated with response to serotonin receptor antagonist (ondansetron) measured by mean drinks per drinking day and percentage days abstinent
	Anxiety	• Lenze (2010), RCT	Variant associated with level of response to SSRI (escitalopram)
	Bipolar disorder	• Biernacka (2012), meta-analysis • Daray (2010), meta-analysis	Inconsistent results, with 1 study finding variant associated with antidepressant-induced mania and 1 study finding insufficient evidence due to heterogeneity between studies
	Depression	• Lewis (2011), RCT • Porcelli (2012), meta-analysis • Seripa (2015), cohort	• RCT results showed response to SSRI (citalopram) and NARI (reboxetine) similar irrespective of presence of variant Meta-analysis results: • Among whites, variant may predict

Gene	Condition	Evidence	Conclusions
			antidepressant response and remission • Among Asians, variant did not predict antidepressant response or remission • Cohort study results showed association between variants and response to SSRIs (escitalopram, sertraline, paroxetine, citalopram)

ADHD: attention deficit/hyperactivity disorder; NARI: norepinephrine uptake inhibitor; RCT: randomized controlled trial; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Management changes that might be made in response to genetic testing information include a selection of specific medications according to test results, discontinuation of medications, and changes in dosing of medications. However, management changes made in response to genetic testing information are not well-defined and may vary according to the judgment of the treating clinician. Currently, there are no specific recommended changes in management linked to specific test results, making it difficult to assess whether test results lead to improvements in health outcomes.

Systematic Reviews

Rosenblat et al (2017) and Health Quality Canada (2017) conducted systematic reviews of RCTs and non-RCTs evaluating whether pharmacogenetics testing improves clinical outcomes for major depressive disorder. Study quality was assessed using the Newcastle-Ottawa Scale in Rosenblat and the GRADE system in Health Quality Canada. Overall, the studies were assessed as low quality, because many were open-label, nonrandomized, and industry-sponsored. Also, many of the estimates were imprecise. Pooled analyses were not conducted in either review. Key studies included in the reviews and trials published after the reviews are described below.

Randomized Controlled Trials

Bradley et al (2018) conducted an RCT in which 685 patients with depression and/or anxiety disorders were randomized to treatment guided by either NeuroIDgenetix or standard of care (see Table 3). Outcomes included HAMD and the Hamilton Rating Scale for Anxiety (HAMA) and adverse drug events. Trained and

blinded clinicians conducted interviews using the HAMD and HAMA. Changes in Hamilton scores are presented in Table 4. The frequency of adverse drug events did not differ statistically between groups.

Olson et al (2017) conducted an RCT in which patients with neuropsychiatric disorders were randomized to treatment guided by NeuroIDgenetix or standard of care (see Table 3). Outcomes included Neuropsychiatric Questionnaire, Symbol Digit Coding test, and adverse drug events. The Neuropsychiatric Questionnaire is a computerized survey addressing symptoms of neuropsychoses, and the SCD assesses attention and processing speed, which is sensitive to medication effects. There were no significant differences in Neuropsychiatric Questionnaire or Symbol Digit Coding scores between groups (see Table 4). However, the patients receiving standard of care reported significantly more adverse events (53%) than patients receiving NeuroIDgenetix-guided care (28%).

Perez et al (2017) conducted an RCT of patients diagnosed with major depressive disorder randomized to genotype-guided treatment (Neuropharmagen) or treatment as usual (see Table 3). The pharmacogenetics report from Neuropharmagen provided information on 50 drugs, highlighting gene-drug interactions and drug recommendations from the FDA and Clinical Pharmacogenetics Implementation Consortium. The primary outcome was Patient Global Impression of Improvement (PGI-I), which was collected by telephone interviewers blinded to treatment allocation group. A response was defined as a PGI-I of 2 or less. Percent responders differed nominally between groups (p=0.05) at the end of the 12-week study (see Table 4). Changes in 17-item HAMD (HAMD-17) scores were significant at 5 weeks (p=0.04) but not at 12 weeks (p=0.08).

A small RCT by Winner et al (2013) evaluated the effect of providing the GeneSight test on the management of psychotropic medications used for major depressive disorder in a single outpatient psychiatric practice (see Table 3). Fifty-one subjects were enrolled and randomized to treatment as usual or treatment guided by GeneSight testing. All subjects underwent GeneSight testing, though results were not given to the physicians in the treatment as usual group until after study completion. At 10-week follow-up, treating physicians dose-adjusted subjects' medication regimens with the same likelihood in the GeneSight group (53%) and the treatment as usual group (58%; p=0.66). However, patients in the GeneSight group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely than those with the same classification in the unguided group to have a medication change or dose adjustment (100% vs 50% respectively; p=0.02). Depression outcomes, measured by the HAMD-17 score, did not differ significantly between groups at the 10-week follow-up (see Table 4). This trial's small size may have limited the ability to detect a significant effect.

Table 3. Summary Characteristics of RCTs Assessing Depression and Anxiety

Study	Country	Sites	Dates	Participants	Interventions	
					Active	Comparator
Bradley et al (2018)	U.S.	20	2016	Patients with depression and/or anxiety disorders	Treatment guided by NeuroIDgenetix (n=352)	SOC (n=333)
Olson et al	U.S.	6	2015	Patients with ADHD, anxiety,	Treatment guided by	SOC (n=59)

Study	Country	Sites	Dates	Participants	Interventions	
(2017)				depression, or psychosis	NeuroIDgenetix (n=178)	
Perez et al (2017)	Spain	18	2014-2015	Patients with MDD according to DSM-IV-TR	Treatment guided by Neuropharmagen (n=136)	SOC (n=161)
Winner et al (2013)	U.S.	1	NR	Patients with major depressive disorder	Treatment guided by GeneSight (n=26)	SOC (n=25)

ADHD: attention-deficit/hyperactivity disorder; DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders*; MDD: major depressive disorder; NR: not reported; RCT: randomized controlled trial; SOC: standard of care.

Table 4. Summary Results of RCTs Assessing Depression and Anxiety

Study	Outcomes					
	Percent Change in HAMD and HAMA Scores (SD)					
	4 Weeks	**p**	**8 Weeks**	**p**	**12 Weeks**	**p**
Bradley et al (2018)						
Patients with anxiety or depression/anxiety						
NeuroIDgenetix	-27 (31)		-45 (33)		-51 (33)	
Standard of care	-34 (32)	0.05	-37 (33)	0.02	-44 (33)	0.06
Patients with anxiety only						
NeuroIDgenetix	-39 (32)		-47 (32)		-54 (35)	
Standard of care	-26 (31)	0.004	-35 (35)	0.02	42 (34)	0.02
	Mean Neuropsychiatric Questionnaire[a]					
	30 Days	**p**	**60 Days**	**p**	**90 Days**	**p**
Olson et al (2017)						
NeuroIDgenetix	108		100		92	
Standard of care	113	*NS*	106	*NS*	95	*NS*
	Percent Responders (PGI-I ≤2)					
	4 Weeks	**p**	**8 Weeks**	**p**	**12 Weeks**	**p**
Perez et al (2017)						
Neuropharmagen	28.5%		40.6%		47.8%	
Standard of care	32.0%	*NS*	37.4%	*NS*	36.1%	0.05
	Percent Change in 17-Item HAMD Scores (SD)					
	4 Weeks	**p**	**6 Weeks**	**p**	**8 Weeks**	**p**
Winner et al (2013)						
GeneSight	-28.3 (NR)		-35.4 (NR)		-30.8 (NR)	
Standard of care	-19.8 (NR)	0.27	-18.5 (NR)	0.04	-20.7 (NR)	0.29

HAMA: Hamilton Rating Scale for Anxiety; HAMD: Hamilton Rating Scale for Depression; NR: not reported; NS: not significant; PGI-I: Patient Global Impression of Improvement; RCT: randomized controlled trial.
[a] Estimated from graph.

Nonrandomized Studies

Two comparative, nonrandomized studies compared clinical outcomes in patients with and without genetic testing. Hall-Flavin et al (2013) presented results from an open-label, nonrandomized comparative trial to evaluate the effects of providing the GeneSight pharmacogenomics test results to inform the management of psychotropic medications used for major depressive disorder in outpatient psychiatric practice. Patients with major depressive disorder were enrolled and grouped consecutively into a “guided” group (n=113) or “unguided” group (n=114). All subjects had DNA samples collected and sent for the GeneSight test, though

only providers for the "guided" group received results. Based on results from patients' genotypes for *CYP2D6*, *CYP2C19*, *CYP1A2*, *SLC6A4*, *and HTR2A*, the test generates a "proprietary interpretive report" that includes recommendations for "use as directed," "use with caution," or "use with caution and with more frequent monitoring" for each of 26 antidepressant and antipsychotic agents. Subjects were followed for 8 weeks—93 patients in the unguided group and 72 patients in the guided group completed follow-up (27% drop out rate). Reviewers found a greater reduction in symptoms in the guided group than in the unguided group for: HAMD-17 ($p<0.001$), the Quick Inventory of Depressive Symptomatology–Clinician Rated ($p<0.001$), and the Patient Health Questionnaire ($p=0.002$). Patients in the guided group had higher rate of remission (26.4%) as measured by the Quick Inventory of Depression Symptomatology–Clinician Rated than in the unguided patients (12.9%; odds ratio,2.42; 95% CI, 1.09 to 5.39; $p=0.03$). Patients in the guided group who were initially on a medication classified as "use with caution and with more frequent monitoring" were more likely (93.8%) than those with the same classification in the unguided group (55%) to have a medication change or dose adjustment during the study period ($p=0.01$).

In an earlier nonrandomized pilot study, Hall-Flavin et al (2012) compared outcomes for a group of patients who had major depression whose physicians received a GeneSight report with those of a historical control group of patients treated without the GeneSight report. Twenty-six subjects were included in the "unguided" group and 25 in the "guided" group. At 8 weeks of follow-up, patients in the guided group had a 31.2% lower Quick Inventory of Depression Symptomatology–Clinician Rated score compared with a 7.25% lower score in the unguided group ($p=0.002$); for HAMD-17 scores, the guided group had a 30.8% lower score while the unguided group had 18.2% lower score ($p=0.04$).

To address the issue of small samples sizes, Altar et al (2015) conducted pooled analyses of the 2 Hall-Flavin (2013, 2012) studies and the RCT by Winner (2013). Included in the pooled analyses were 119 patients receiving GeneSight-guided treatment and 139 receiving usual care. Patients who received a "red" score on the basis of the GeneSight algorithm ("use with increased caution and with more frequent monitoring") had less improvement in HAMD-17 scores over 8 weeks than patients with "yellow" scores ("use with caution") or "green" scores ("use as directed"), or yellow/green for subjects prescribed cytochrome P450 2D6 (CYP2D6) substrate medications ($p=0.001$, $p=0.01$, $p=0.002$, respectively) and for subjects prescribed CYP2C19 substrate medications ($p=0.003$, $p=0.02$, $p=0.004$, respectively). None of the single genes included in the GeneSight panel was individually associated with positive or negative treatment outcomes. The odds for clinical response, defined as a 50% or greater decrease in HAMD score, was significant, favoring the patients receiving GeneSight-guided treatment (2.3; 95% CI, 1.3 to 3.9). The odds ratio for clinical remission, defined as achieving a score of 7 or less on the HAMD score, was not significant (1.8; 95% CI, 0.9 to3.4).

Breitenstein et al (2014) reported on results of a small nonrandomized comparative study assessing whether genotyping of the *ABCB1* gene in clinical practice was associated with changes in medication management in outcomes among 58 patients hospitalized with depression. Patients and matched controls were selected from the Munich Antidepressant Response Signature project, a naturalistic study designed to

identify factors that help to predict and improve treatment response in affective disorders. *ABCB1* genotyping was implemented into the study's protocol in 2008, and genotype results were provided to treating physicians with a 1-page letter outlining potential strategies based on genotype. The 58 patients who had *ABCB1* genotyping were compared with a matched sample of historical controls enrolled before genotyping was implemented. Patients who received *ABCB1* genotyping had higher remission rates at hospital discharge (83.6% vs 62.1%, p=0.005) and lower HAMD scores at hospital discharge (scores extrapolated from the graph, 6 vs 8; p=0.02). This study was limited to hospitalized patients with assessment of outcomes limited was to the time of hospital discharge.

Retrospective Studies
Brennan et al (2015) presented a case series of 685 patients who underwent testing with the Genecept Assay, with the results provided to participating clinicians. Approximately 70% and 29% of patients had primary diagnoses of a mood or an anxiety disorder, respectively. Eighty-seven percent of patients showed improvement (defined as very much improved, much improved, or minimally improved), and 62% showed very much or much-improved status.

Espadeler et al (2016) reported on the results of a retrospective series of psychiatric patients who underwent testing with a pharmacogenetic test (Neuropharmagen) marketed in Europe. Patients whose treatment was considered to follow the test recommendations were compared with those whose treatment did not. Criteria for determining whether a patient's treatment followed recommendations were complex. Outcomes were assessed by the treating psychiatrist who determined whether the patient improved over baseline. At 3-month follow-up, 93% (83/89) patients whose treatment followed the recommendations had improved compared with 82% (76/93) those whose treatment did not (p=0.019).

Section Summary: Clinically Useful
Four RCTs testing 3 different genetic panels were identified. After 8 to 12 weeks of follow-up, the largest RCT showed significant improvements in HAMD and HAMA scores among patients whose clinicians were guided by information from genetic tests. However, results in the remaining 3 trials did not show differences between test-guided and -unguided groups. Nonrandomized studies have reported significant improvements in outcomes among patients receiving guided treatment, but weaknesses in the studies such as large loss to follow-up, no comparison group, and small sample sizes limit the conclusions that can be drawn. Additional studies including larger numbers of patients with randomization and blinded outcome assessment will be needed to confirm findings that genotyping may be associated with improved clinical outcomes.

SUMMARY OF EVIDENCE
For individuals who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, the evidence includes various observational studies (case-control, genome-wide association study) evaluating the association between the mental illness of interest and candidate genes. Relevant outcomes are test validity, other test performance measures, and changes in disease status. Most

studies have evaluated the association between genotype and mental health disorders without a clinical perspective; thus diagnostic characteristics and validated risk predictions among specific clinical populations are unknown. The associations are inconsistent across studies. There is no clear clinical strategy for how the associations of specific genes and mental health disorders would be used to diagnose a specific patient or to manage a patient at higher risk of a specific disorder. No studies were identified that evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a mental illness who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a large number of observational studies assessing specific genes and outcomes of drug treatment, as well as 4 RCTs and several observational studies comparing outcomes for patients who received treatment guided by genetic testing with patients who received standard of care treatment. Relevant outcomes are symptoms, changes in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. A large RCT showed that patients receiving treatment guided by genetic test results experienced significant improvements in mental health scores; however, the remaining RCTs showed no difference in mental health outcomes. Observational studies comparing patients who have had and have not had genetic testing reported that testing may be associated with differences in depression treatment outcomes, though methodologic shortcomings such as lack of randomization, small sample sizes, and large loss to follow-up limit the conclusions that can be drawn. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 01/15/2014
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01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. New policy.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Title changed from Genecept Assay to Genetic Testing for Mental Health Conditions. Entire policy rewritten to track BCBSA.
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Policy statements changed to clarify which categories of genetic testing the policy addresses.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval . No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval . No change to coverage.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Policy statements changed to specify drugs used to treat mental health conditions (SSRIs, SNRIs, tricyclic antidepressants, and antipsychotic drugs). Title changed to “Genetic Testing for Diagnosis and Management of Mental Health Conditions.”
10/01/2018	Coding update

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0032U, 0033U, 81225, 81226, 81230, 81231, 81291, 81401, 81479 Codes added eff 10/1/18: 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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